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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/899,575	ZUR MEGEDE ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38 and 78-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38 and 78-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 July, 2001,* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply..*.

Detailed Office Action

Status of the Claims

Acknowledgement and entry of the communication filed 10 December, 2007, is hereby made. Claims 38 and 78-90 are pending in the instant application. Claims 78-90 stand withdrawn as being directed toward a non-elected invention. Applicants requested rejoinder of these claims in response to the *Ex parte Quayle* notice sent out in the last office action. After careful reconsideration of the claimed subject matter and consultation with a Biotechnology Center 1600 Practice Specialist, the allowability of claim 38 has been withdrawn and new grounds of rejection set forth below. However, in an effort solely to expedite prosecution in this application, the examiner has agreed to rejoin method claims 78-90 with claim 38. Thus, claims 38 and 78-90 are currently under examination.

35 U.S.C. § 120 Benefit

Acknowledgement is hereby made of applicants priority claim under 35 U.S.C. § 120. Perusal of the application relied upon demonstrates that U.S. Serial No. 09/610,313, filed 05 July, 2000, fails to provide support for the claimed expression cassette. Specifically, the '313 application fails to disclose a modified HIV-1 Env consisting of SEQ ID NO.: 120. Accordingly, for the purposes of applying prior art, this application has been afforded an effective filing date of 05 July, 2001.

37 C.F.R. § 1.821-1.825

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2) (e.g., see pages 23-25 and 28 of the specification). However, this application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicants are reminded that sequences appearing in the specification and/or **drawings** Applicant is reminded that sequences appearing in the **specification** and/or drawings (e.g., see p. 3 (GPGR); p. 17 (YMDD); p. 107, Table 4; Figure 7 (YMDD/WMGY)) and/or claims must be identified by a sequence identifier (SEQ ID NO.:) in accordance with 37 C.F.R. . 1.821(d). Sequence identifiers for sequences appearing in the drawings may appear in the Brief Description of the Drawings. Applicant must provide appropriate amendments to the specification and/or drawings inserting the required sequence identifiers. Extensive amendments may necessitate the submission of a substitute specification and drawings.

Specification, Objections

The specification is objected to because of the following informalities: Applicants are reminded that viral genes are designated by lowercase italics (e.g., the *gag* gene; *gag* encodes a 55 kDa structural protein) whereas viral gene products are capitalized (e.g., the Gag protein; Gag is a structural protein involved in virion assembly and morphogenesis) (see 2008 Instructions to Authors, J. Virol.). There are numerous instances in the specification where it is not readily manifest if applicants are referencing the viral gene or gene product

(e.g., see pp. 1, 2, 4, 5, 7, 8, 49, 50, 55, 73-78, and 93). All of these pages incorrectly reference viral genes/gene products. Appropriate correction is required. Extensive revisions may necessitate the submission of a substitute specification.

Drawings Objected To

The drawings are objected to because figure 105 is illegible. Corrected drawing sheets in compliance with 37 C.F.R. § 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 C.F.R. § 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 38 and 78-90 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). *In re Rochester*, 358 F.3d 916, 69 U.S.P.Q.2d 1886 (C.A.F.C. 2004). Claim 38 is directed toward an expression cassette comprising a polynucleotide encoding an immunogenic Env polypeptide having at least 90% identity to the full-length sequence set forth in SEQ ID NO.: 120. Claims 78-90 are directed toward immunization methods employing said expression cassette. The specification discloses the isolation and preliminary characterization of three novel HIV-1 clade C South African isolates designated 8_5_TV1-C.ZA, 8_2_TV1_C.ZA, and 12-5_1_TV2_C.ZA. SEQ ID NO.: 120 encodes a codon-optimized gp140 envelope glycoprotein with a modified signal sequence and a deletion of the V2 region obtained from isolate 8_2_TV1_C.ZA. This modified Env is approximately 630 amino acids in length. Appropriately drafted claim language directed toward SEQ ID NO.: 120 would be acceptable (i.e., An expression cassette comprising a polynucleotide sequence encoding a codon-optimized modified HIV-1 Env glycoprotein comprising SEQ ID NO.: 120). However, the skilled artisan would reasonably conclude that applicants

were not in possession of the broad genus of compounds directed toward any sequence displaying up to 10% genetic unrelatedness to the parent sequence.

The crux of the statutory requirement governing written description is whether one skilled in the art, familiar with the practice of the art at the time of the filing date, could reasonably have found the later claimed invention in the specification as filed. *In re Kaslow*, 707 F.2d 1366, 1375, 217 U.S.P.Q. 1089, 1096 (Fed. Cir. 1983). *In re Wilder*, 736 F.2d 1516, 1520 222 U.S.P.Q. 349, 372 (Fed. Cir. 1984, *cert. denied*, 469 U.S. 1209 (1985). *Texas Instruments, Inc.* v. *International Trade Comm'n*, 871 F.2d 1054, 1063, 10 U.S.P.Q.2d 1257, 1263 (Fed. Cir. 1989). Moreover, the courts have stated that the evaluation of written description is highly fact-specific, and that broadly articulated rules are inappropriate. *In re Wertheim*, 541 F.2d 257, 263, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976). *In re Driscoll*, 562 F.2d 1245, 1250, 195 U.S.P.Q. 434, 438 (C.C.P.A. 1977). It is also important to remember that the true issue in question is not whether the specification enables one of ordinary skill in the art to make the later claimed invention, but whether or not the disclosure is sufficiently clear that those skilled in the art will conclude that the applicant made the invention having the specific claim limitations. *Martin* v. *Mayer*, 823 F2d 500, 505, 3 U.S.P.Q.2d 1333, 1337 (Fed. Cir. 1987).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor has **possession** of the claimed invention. See, e.g., *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116. An applicant shows possession of the claimed invention by describing the claimed invention with all

of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood* v. *American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. *Fujikawa* v. *Wattanasin*, 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1996).

The skilled artisan would reasonably conclude that applicants were not in possession of the claimed invention for the following reasons: First, the claims encompass an inordinate number of nucleotide and polypeptide variants. SEQ ID NO.: 120 is 1,986 nucleotides in length and gp140mod.TV1.delV2 is approximately 630 amino acids in length. The claims encompass any sequence that is at least 90% genetically related to the parent sequence. This level of genetic variation at the nucleotide sequence level would encompass approximately $(3^{199})(1986!)/(199!)(1786!)$ or ~1 x 10^{835} variants. Ten percent genetic variation at the amino acid sequence level would result

in ~1 x 10^{171} variant polypeptide sequences.[1] Thus, the number of variant polynucleotide and amino acid sequences encompassed by the claim language is clearly beyond the scope of reasonable experimentation. Second, considering the enormous claim breadth, it would require more than a single nucleotide sequence encoding a modified Env to provide adequate support. However, the disclosure does not describe the isolation and characterization of a single variant obtained from SEQ ID NO.: 20. There is no indication from review of the disclosure that applicants isolated and characterized and variant sequences. Third, the claims are directed toward polynucleotides encoding "immunogenic" Env polypeptides. The term immunogenic is clearly directed toward an immunogen that is capable of inducing a humoral and/or cell-mediated ($CD4^+$ or $CD8^+$) immune response to the immunogen of interest (see specification, pages 30-31). However, the disclosure fails to identify a single humoral epitope, T-helper epitope, or cytotoxic T-lymphocyte epitope of interest. There is no discussion of which epitopes can tolerate various amino acid substitutions, additions, or deletions. Thus, nothing in the disclosure leads the skilled artisan to any particular nucleotide or amino acid sequence. Once again, there is no evidence in the disclosure to suggest that applicants ever isolated or characterized any epitopic variants. Fourth, it has been well-documented that single or multiple amino acids substitutions, additions, or deletions can abrogate humoral, T-helper, and cytotoxic T-lymphocyte epitope recognition (Johnson *et al.*, 1992; Dai *et al.*, 1992; Watkins *et al.*, 1993; Fenoglio

[1] These calculations were performed as follows: $TV=(N^Y)(X!)/(Y!)((X-Y-1)!)$, wherein, TV=the total number of variant sequences, N=the number of amino acids or nucleotides that can be substituted (i.e., if any of the 20 naturally occurring amino acids can be substituted, N=19; if any of the four naturally occurring nucleotides can be substituted, N=3), Y=the number of amino acids/nucleotides in the parent sequence that can be substituted (i.e., if the amino acid sequence is 100 aa in length and 10% genetic variation is allowed, Y=10 [100@10%]), and X=the total sequence length of the sequence of interest.

et al., 2000; McLain *et al*., 2001; Liu *et al*., 2006). Thus, the art is highly unpredictable and the skilled artisan cannot predict *a priori* the effects of any given substitution on the immunologic properties of the Env polypeptide. Finally, the case law suggests that applicants must provide more than one or two examples to put them in possession of a large genus. See *In re Gosteli*, 10 U.S.P.Q.2d 1614 (Fed. Cir. 1989) and *Ex parte Kubin*, 83 U.S.P.Q.2d 1410 (Bd. Pat. App. & Int. 2007). Therefore, when all the aforementioned factors are considered *in toto*, the skilled artisan would reasonably conclude that applicants were not in possession of the full genus of variants.

Scope of Enablement

Claim 38 is rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Claim 38 is directed toward an expression cassette comprising a polynucleotide encoding an immunogenic Env polypeptide having at least 90% identity to the full-length sequence set forth in SEQ ID NO.: 120. The specification discloses the isolation and preliminary characterization of three novel HIV-1 clade C South African isolates designated 8_5_TV1-C.ZA, 8_2_TV1_C.ZA, and 12-5_1_TV2_C.ZA. SEQ ID NO.: 120 encodes a codon-optimized gp140 envelope glycoprotein with a modified signal sequence and a deletion of the V2 region obtained from isolate 8_2_TV1_C.ZA. This modified Env is approximately 630 amino acids in length. Appropriately drafted claim language directed toward SEQ ID NO.: 120 would be acceptable (i.e., An expression cassette comprising a polynucleotide sequence encoding a codon-optimized modified

HIV-1 Env glycoprotein comprising SEQ ID NO.: 120). However, the skilled artisan would reasonably conclude that applicants' disclosure fails to support the full claim breadth desired.

The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The claim breadth encompasses an inordinate number of polynucleotide and amino acid sequences. SEQ ID NO.: 120 is 1,986 nucleotides in length and gp140mod.TV1.delV2 is approximately 630 amino acids in length. As previously discussed, the claims encompass any sequence that is at least 90% genetically related to the parent sequence. This level of genetic variation at the nucleotide sequence level would encompass approximately $(3^{199})(1986!)/(199!)(1786!)$ or ~1 x 10^{835} variants. Ten percent genetic variation at the amino acid sequence level would result in ~1 x 10^{171} variant polypeptide sequences.[2] Thus, the number of variant polynucleotide and amino

[2] Ibid.

acid sequences encompassed by the claim language is clearly beyond the scope of reasonable experimentation.

2) The disclosure fails to provide adequate guidance pertaining to the acceptability of any given amino acid substitution, addition, or deletion. Humoral and cell-mediated epitopes may be linear or conformational. In addition to those sequences comprising the epitope itself, flanking cellular sequence can also influence the immunogenicity of an epitope. However, the disclosure fails to lead the skilled artisan to any particular embodiments. There is no discussion of epitopes of interest and the modifications that will retain or increase Env immunogenicity.

3) The prior art clearly demonstrates that the skilled artisan cannot predict *a priori* the effects of any given amino acid substitution, addition, or deletion on epitope processing and recognition. It has been well-documented that single or multiple amino acids substitutions, additions, or deletions can abrogate humoral, T-helper, and cytotoxic T-lymphocyte epitope recognition (Johnson *et al.*, 1992; Dai *et al.*, 1992; Watkins *et al.*, 1993; Fenoglio *et al.*, 2000; McLain *et al.*, 2001; Liu *et al.*, 2006). Once again, the disclosure fails to provide any guidance pertaining to acceptable changes that can be made to the envelope glycoprotein.

4) The disclosure fails to provide any working embodiments. As discussed in items one through three, the claims encompass an inordinate number of nucleotide and polypeptide sequence variants. Considering the unpredictability of the art, a reasonable number of embodiments would be required to enable the full claim breadth. However, the disclosure fails to describe the creation of a single variant. The disclosure fails to identify any eptiopic or other structural regions of interest.

Thus, the specification clearly fails to provide any working embodiments.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the invention in a manner commensurate in scope with the claims.

Enablement

Claims 78-90 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 78-90 are directed toward immunization methods employing an expression cassette comprising a polynucleotide encoding an immunogenic Env polypeptide having at least 90% identity to the full-length sequence set forth in SEQ ID NO.: 120. The specification discloses the isolation and preliminary characterization of three novel HIV-1 clade C South African isolates designated 8_5_TV1-C.ZA, 8_2_TV1_C.ZA, and 12-5_1_TV2_C.ZA. SEQ ID NO.: 120 encodes a codon-optimized gp140 envelope glycoprotein with a modified signal sequence and a deletion of the V2 region obtained from isolate 8_2_TV1_C.ZA. This modified Env is approximately 630 amino acids in length. The term immunize is art-recognized and generally references a humoral and/or cell-mediated immune response that leads to a preventative or therapeutic response against the pathogen of interest. Thus, administration of the claimed expression cassettes for immunization purposes requires that the immune response of interest must be prophylactic or therapeutic.

The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The claim breadth encompasses an inordinate number of polynucleotide and amino acid sequences. SEQ ID NO.: 120 is 1,986 nucleotides in length and gp140mod.TV1.delV2 is approximately 630 amino acids in length. As previously discussed, the claims encompass any sequence that is at least 90% genetically related to the parent sequence. This level of genetic variation at the nucleotide sequence level would encompass approximately $(3^{199})(1986!)/(199!)(1786!)$ or ~1 x 10^{835} variants. Ten percent genetic variation at the amino acid sequence level would result in ~1 x 10^{171} variant polypeptide sequences.[3] Thus, the number of variant polynucleotide and amino acid sequences encompassed by the claim language is clearly beyond the scope of reasonable experimentation.

[3] Ibid.

2) The disclosure fails to provide adequate guidance pertaining to the acceptability of any given amino acid substitution, addition, or deletion. Humoral and cell-mediated epitopes may be linear or conformational. In addition to those sequences comprising the epitope itself, flanking cellular sequence can also influence the immunogenicity of an epitope. However, the disclosure fails to lead the skilled artisan to any particular embodiments. There is no discussion of epitopes of interest and the modifications that will retain or increase Env immunogenicity.

3) The prior art clearly demonstrates that the skilled artisan cannot predict *a priori* the effects of any given amino acid substitution, addition, or deletion on epitope processing and recognition. It has been well-documented that single or multiple amino acids substitutions, additions, or deletions can abrogate humoral, T-helper, and cytotoxic T-lymphocyte epitope recognition (Johnson *et al.*, 1992; Dai *et al.*, 1992; Watkins *et al.*, 1993; Fenoglio *et al.*, 2000; McLain *et al.*, 2001; Liu *et al.*, 2006). Once again, the disclosure fails to provide any guidance pertaining to acceptable changes that can be made to the envelope glycoprotein.

4) The disclosure fails to provide any working embodiments. As discussed in items one through three, the claims encompass an inordinate number of nucleotide and polypeptide sequence variants. Considering the unpredictability of the art, a reasonable number of embodiments would be required to enable the full claim breadth. However, the disclosure fails to describe the creation of a single variant. The disclosure fails to identify any eptiopic or other structural regions of interest. Thus, the specification clearly fails to provide any working embodiments.

5) The prior art teaches unequivocally that to date, all HIV-1 immunization regimens have failed to produce a prophylactic or therapeutic immune response (Burton and Moore, 1998; Desrosiers, 2004; Pantaleo and Koup, 2004). This is due to several factors including the genetic variation, or quasispecies nature of HIV-1 and -2 infection, which leads to immune escape. A lack of understanding of the correlates of human protection. A lack of understanding of which immunogens/adjuvants and immunization regimens will produce correlates of protection. The failure of animal models to accurately predict vaccine efficacy. The ability of the virus to integrate into the host genome thereby becoming a lifelong event. The ability of the virus to induce ineffective immune responses. It seems rather unlikely that an efficacious HIV-1 vaccine will become available in the near or distant future.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the invention in a manner commensurate in scope with the claims.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Bruce R. Campell, Ph.D., can be reached at (571) 272-0974. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908 or at Jeffrey.Parkin@uspto.gov.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the

Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

/Jeffrey S. Parkin, Ph.D./
Primary Examiner, Art Unit 1648

22 March, 2008